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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/302,896	04/30/1999	MICHAEL B. CHANCELLOR	2710-4007-US	7603

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EXAMINER
KAUSHAL, SUMESH

ART UNIT	PAPER NUMBER
1636	14

DATE MAILED: 10/24/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/302,896	CHANCELLOR ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 July 0902* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-118* is/are pending in the application.

4a) Of the above claim(s) *15-42,49-80,82,103,105,117 and 118* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14, 43-48, 81, 83-102, 104, 106-116* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's response filed on 07/09/02 has been acknowledged.

Claims 1-118 are pending.
Claims 15-42, 49-80, 82, 103, 105, 117 and 118 are withdrawn from further consideration
Claims 1-14, 43-48, 81, 83-102, 104, 106-116 are examined in this office action.

► *If the claims are amended, added and/or canceled in response to this office action the applicants are required to follow Amendment Practice under 37 CFR § 1.121 (http://www.uspto.gov) and A CLEAN COPY OF ALL PENDING CLAIMS IS REQUESTED.*

Election/Restrictions

Applicant's election with traverse of Group-1, method of treating Urinary Stress Incontinence (Claims 1-14, 43-48, 81, 83-102, 104, 106-116), wherein in addition to iNOS and IL-1Ra the elected growth factor is an insulin-like growth factor (IGF) in Paper No. 13 is acknowledged. The traversal is on the ground(s) that groups 1-3 are classified in same class and subclass and it is believed that a search can be carried out on combinations of groups. The applicant further argues that various cytokines and factors that can be used to ameliorate genitourinary tract dysfunction when used in conjunction with the claimed methods of group 1-3. This is not found persuasive because a) Urinary stress incontinence b) Bladder inflammation and c) Erectile dysfunction are located at different sites in the urinary tract and have different modes of operation. For example, urinary stress incontinence is caused by dysfunctional sphincter muscle, Bladder inflammation leads to defects in bladder contraction, whereas erectile dysfunction is only limited to male population. In addition, different growth factors and cytokines have different function and effects. The method of treatment would require different sites of

action, which have different functions. In addition, claims 63-68 belong to an un-elected group, which have different uses (making recombinant proteins). Furthermore searching of one group would not over the subject matter of other groups and therefore would require additional search. Therefore there is a search burden to examine all the groups is one single invention.

The requirement is still deemed proper and is therefore made FINAL.

Claims 15-42, 49-80, 82, 103, 105, 117 and 118 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected invention(s), there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 13.

Claims 10 and 114 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 13.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-14, 43-48, 81, 83-102, 104, 106-116 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, **to make and/or use the invention**.

The instant claims are drawn to a method of treating urinary stress incontinence by repairing injured genitourinary tract tissue by administering genetically engineered

muscle derived cells which encodes a bioactive molecule. The instant claims are further drawn to the method wherein the bioactive molecule is inducible nitric oxide synthase (iNOS) and/or a growth factor, wherein the growth factor is an insulin-like growth factor (IGF). In addition the claims are drawn to a method of repairing sphincter muscle injury or dysfunction by administering muscle derived cells, wherein the cell are genetically engineered to contain nucleic acid encoding a heterologous bioactive gene product (growth factor, IGF).

The instant specification teaches the injection of genetically engineered GH8 myoblast cell line expressing b-galactosidase into the urethral wall of adult female rat with cryo-induced uretheral injury (page 54, example-2, table-1). The specification further teaches injection of the genetically engineered myoblast cells expressing b-galactosidase and iNOS into the dome of the bladder and into left and right lateral walls near the dome (page 57, example-3, table-2). The specification concluded that these experiments demonstrated an alteration of bladder and urethral function with cyro-injury model (spec. page 59, line 5). The specification further teaches the injection of myoblasts expression iNOS gene resulted in the release of NO at the site of injection site in penis and bladder but fails to disclose that release of NO resulted in the treatment of urinary stress incontinence especially in patients with afferent nerve induced micturition reflexes (spec. page 79, lines 14-24, *infra Young et al*). Similarly the specification teaches that IGF-1 promotes muscle growth in vitro, but fails to disclose that over expression of IGF-1 would lead to the treatment of the treatment of urinary stress incontinence especially in patients with afferent nerve induced micturition reflexes (spec. page 83, line 5, *infra Young et al).*

The scope of instant invention as claimed encompasses repairing any and all sites in the genitourinary tract tissue by injecting any and all muscle derived cells which are genetically engineered to express any and all bioactive molecules, to improve or alleviate urinary stress incontinence.

- However, the instant specification fails to disclose that injection of genetically engineered cells into any and all sites of the genitourinary tract would lead to the treatment of urinary stress incontinence.

- The instant specification fails to disclose that that injection of any and all types of cells derived from any and all types of muscles into the genitourinary tract would lead to the treatment of urinary stress incontinence.
- The instant specification fails to disclose that injection of genetically engineered cells expressing any and all bioactive compounds would lead to the treatment of urinary stress incontinence.
- The instant specification fails to disclose that injection of genetically engineered cells expressing any and all tropic factors (growth factors, especially IGF-1) would lead to the treatment of urinary stress incontinence.
- The instant specification fails to disclose that injection of genetically engineered cells expressing any and all immune suppression factor would lead to the treatment of urinary stress incontinence by allowing survival of injected cells and prevent an adverse immune response.
- The instant specification fails to disclose that injection of any and all type of muscle derived stem cells (like erythrocytes derived from muscle blood vessels) would lead to the treatment of urinary stress incontinence.
- The instant specification fails to disclose any method that repairs the spinchter muscle injury or dysfunction by introducing any and all types of muscle derived cells, wherein the cells are genetically engineered to produce any and all bioactive gene products.

The instant invention is drawn to a method that requires gene-based therapeutics. The Gene therapy is considered highly experimental area of research at this time, and both researchers and the public agree that demonstrable progress to date has fallen short of initial expectations. No cures can as yet be attributed to gene therapy. (Rosenberg et al, Science 287:1751, 2000, Verma, Mol. Ther. 1: 493, 2000, Friedmann, Science 287(5461):2163-5, 2000, Anderson WF, Nature 392:25-30, 1998; Verma et al Nature 389:239-242, 1997, Touchette, Nat. Med. 2(1) 7-8, 1996). None of the human studies to date has shown definite efficacy, despite more than 300 protocols involving 3000 patients since September 1990 (Anderson page 25 col.1 para.1). Most studies have neglected to

include well-defined biochemical or clinical end points that would clearly indicate whether the therapy is having a desired effect. For example, in original clinical trial to treat adenosine deaminase (ADA) deficiency, patients received a total of 11 infusions of genetically modified autologous T-lymphocytes along with polyethylene glycol (PEG)-ADA. After 7 years of therapy no definitive conclusion is drawn as to the contribution of gene therapy to the present state of health of patients (Touchette, page 7 col.3, para.1; Anderson page 29 col.1, para.6). Furthermore, Recombinant DNA Advisory committee (RAC) also emphasized that expectations of current gene therapy protocols have been over sold without any apparent success (Touchette page 7, col.1 para. 2; page 8, col.2 para 1-4). The advisory panel further emphasized the need for a greater understanding of an underlying mechanism that contribute to a genetic disease along with the pathogenesis of the disease. (Touchette, page 7, col.3, para.3). In instant case the specification fails to disclose a method of treating urinary stress incontinence by repairing any and all sites in the genitourinary tract tissue by injecting any and all muscle derived cells wherein the muscle derive cells are genetically engineered to express any and all bioactive molecules.

The state of the art at the time of filing teaches that urinary stress incontinence occurs when urethral sphincter muscle is not sufficiently strong to prevent urine leakage for example while coughing or jumping. (Chancellor et al, TRENDS in Mol. Med. 7(7):301-306, 2001; see Spec. page 8, lines 15-28). Furthermore, in many patients the urinary incontinence the result of mixed urge and stress incontinence. The uretheral afferent nerve activity affects the micturition reflexes, indicating that in patients with stress urinary incontinence, the leakage of urine into proximal urethra stimulates afferent nerve, which facilitate voiding reflexes (Young et al, The Journal of Urology, 162:204-212, 1999, see abstract, conclusions). The instant specification fails to disclose a method that repairs spinchter muscle injury or dysfunction by introducing genetically engineered cells. Furthermore the specification fails to provide any guidance to treat urinary stress incontinence by modulating the afferent nerve reflexes in patients with mixed urge and stress incontinence conditions. Young et al clearly teaches that in patients with mixed stress and urge incontinence it would be appropriate to treat stress incontinence as a strategy to improve or cure detrusor instability (Young page 209, col.1, para.1).

Therefore considering the instant specification, the applicant fails to disclose that bulking of the spinchter muscle alone would lead to the treatment of urinary stress incontinence, since the urinary stress incontinence is not only caused by the weakening of spinchter muscle but is also the result of afferent nerve reflexes. The state of the art at the time of filing clearly teaches that despite the gene therapy holds much promise to come, the success will only be achieved through continued rigorous research on the most fundamental mechanisms that contribute to a genetic disease along with the pathogenesis of the disease, gene delivery and gene expression in animal.

Thus, in view of lack of specific guidance in the specification, the skilled artesian at the time of filing would be unable to use the claimed invention, without an excessive and undue amount of experimentation. The quantity of experimentation required would include injecting any and all types of muscle derived cells into any and all sites in the genitourinary tract tissue wherein the genetically engineered to express any and all bioactive molecules. The undue experimentation required would further include evaluation of the survival and/or ability of any and all muscle derived cells (as claimed) to deliver the gene product of interest at the implant site. In addition the undue experimentation required would further include the therapeutic effect of any and all bioactive molecules (growth factors and/or immunosuppressive factors) to improve or alleviate urinary stress incontinence.

Claims 1-14, 43-48, 81, 83-102, 104, 106-116 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "muscle derived cells" in claim 1, 2, 8, 13, 43, 44-47, 81, 83, 92, 104, 106-107, 109-113 is a relative term which renders the claim indefinite. The term "muscle derived cell" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. For example, an erythrocyte, a

macrophage or hematopoietic stem cell could be a muscle-derived cell, when theses cells were obtained from the muscle blood vessels.

Claims 3 and 110 are indefinite because it is unclear what is the "muscle-derived stem cells" in this context for same reasons as set forth above.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is (703) 305-6838. The examiner can normally be reached on Monday-Friday from 9:00 AM to 5:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Irem Yucel Ph.D. can be reached on (703) 305-1998. The fax-phone number for the organization where this application or proceeding is assigned as (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst Zeta Adams, whose telephone number is (703) 305-3291.

S. Kaushal
Patent examiner

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER